Remarks

Interview

Applicants and the undersigned greatly appreciate the examiner and her supervisor taking the time and effort to discuss the case in the telephone interview of November 6, 2007. The interview provided the applicants with an opportunity to discuss the basis of the invention; the long standing problem with abuse where users destroy the time-release mechanism of extended release formulations by chewing or crushing them, making the full dose of drug available for oral, nasal or IV administration; and the difficulties in making a formulation that is orally bioavailable but resists crushing and simple methods of extraction. Dr. Fleming explained how much experimentation and research was required to develop a composition which differs from that of the prior art by:

Selection of a lipophilic drug or use of a lipophilic derivative,

And

Incorporation of the lipophililic drug or derivative into a narrow class of lipophilic carriers (not a mixture of materials including a lipophilic carrier), using a technique that produces a uniform dispersion of lipophilic drug in lipophilic carrier,

Which can **then** be further formulated, for example, as a tablet or capsule.

Dr. Fleming also discussed the comparative experiments described in the Declaration under 37 C.F.R. § 1.132 filed July 2007, which compared the amount of active agent that can be extracted from the claimed compositions and the compositions described in the prior art when

the integrity of the composition is compromised. These results demonstrated unexpectedly greater resistance to extraction of the claimed product relative to the commercially available product, which the Declaration demonstrates corresponds to the formulation described in the prior art, minus the additional active ingredient (i.e., the antagonist) that makes the formulation less effective to abusers.

Dr. Fleming also briefly discussed a recent clinical study conducted on two formulations of oxycodone covered by the pending claims. This study included a comparison of the blood levels produced by one of the formulations when swallowed whole (as intended) versus when swallowed after chewing the formulation (a common method of tampering). The study demonstrated that the blood levels produced in humans were similar when the formulation was swallowed intact or after chewing. Thus, it can be expected that misuse by chewing would not result in a spike in plasma level as desired by the abuser. The results of these studies are described in the accompanying Second Declaration under 37 C.F.R. § 1.132.

Claimed Compositions

As discussed during the interview, the claimed compositions contain a lipophilic drug or lipophilic derivative of a drug uniformly dispersed in fats, fatty substances, waxes, wax-like substances, or mixtures thereof. The material can be formulated with one or more pharmaceutically acceptable excipients into a unit dosage form, such as a capsule or tablet. The fact that the lipophilic drug or lipophilic derivative of a drug is uniformly dispersed within the

lipophilic carrier prevents the immediate release of the incorporated drug when the physical integrity of the composition is compromised and the resulting material is exposed to water.

The Prior Art

U.S. Patent No. 6,310,072 Smith

Smith describes a composition containing a sub-analgesic dosage of a μ-agonist and a sub-analgesic dosage of a K_2-opioid agonist (col. 5, lines 5-10). Smith discloses generally "dosage forms include tablets, dispersions, suspensions, injections, solutions, syrups, troches, capsules, suppositories, aerosols, transdermal patches and the like. Controlled release of the strong opioids may be affected by coating the same, for example, with hydrophobic polymers including acrylic resins, waxes, higher aliphatic alcohols, polylactic and polyglycolic acids and certain cellulose derivatives such as hydroxypropylmethyl cellulose. In addition, the controlled release may be affected by using other polymer matrices, liposomes and/or microspheres."

There is no disclosure in Smith of incorporating or dispersing the drug first into a lipophilic or water insoluble carrier.

U.S. Patent No. 6,696,088 to Oshlack

Oshlack describes formulations containing an opioid agonist, such as oxycodone, and a sequestered opioid antagonist, wherein the opioid antagonist is substantially not released when the dosage form is administered **intact** (abstract). If the integrity of the dosage form is compromised, the antagonist is released to reduce the effect of the opioid agonist.

Oshlak does not disclose a lipophilic drug or lipophilic derivative of a drug,

much less lipophilic drug dispersed in a lipophilic carrier as defined in the claims. Further, the compositions described in Oshlak do not prevent immediate release of the active agent when the integrity of the dosage form is compromised. As discussed in Dr. Fleming's first declaration, the compositions described in Oshlak released greater than 95% of the drug after 15 minutes in simulated gastric juices when the integrity of the dosage form was compromised. In contrast, the claimed compositions released less than 32% of the drug after 15 minutes.

U.S. Patent No. 6,048,736 to Kosak

Kosak is similar to Oshlack in disclosing coatings that decrease extraction, but only until the tablet is crushed.

U.S. Patent No. 5,756,483 to Merkus

Merkus describes the nasal administration of a drug in combination with cyclodextrin (preferably methylated beta-cyclodextrin) or polysaccharide in order to improve the stability or bioavailability of the drug. Merkus discloses the formation of a complex between a drug and a poorly water soluble cyclodextrin (e.g., ethylated beta-cyclodextrin) in order to achieve a lipophilic derivative of the drug (See paragraph 0040). Merkus does not disclose or suggest incorporating a lipophilic drug or a lipophilic derivative of a drug into the carrier defined into claim 1. Further, the compositions described in Merkus do not prevent immediate release of the active agent when the integrity of the dosage form is compromised.

Oshlak, Kosak, and Merkus do not cure the deficiencies of Smith. Accordingly, claims 1-23, 26, 27, 29, and 33-40 are not obvious over Smith in view of Oshlak.

Allowance of claims 1-23, 26, 27, 29, and 33-40 is respectfully solicited.

Respectfully submitted,

/Patrea L. Pabst/

Patrea L. Pabst
Reg. No. 31,284

Date: November 15, 2007

PABST PATENT GROUP LLP
400 Colony Square, Suite 1200
1201 Peachtree Street
Atlanta, Georgia 30361
(404) 879-2151
(404) 879-2160 (Facsimile)